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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,801	KING ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-42* is/are pending in the application.

4a) Of the above claim(s) *14-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 04/28/05, 11/18/04, 03/22/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed on December 12, 2003 has been acknowledged. However, the amendment is not in compliance with 37 CFR 1.57(a) because is fails to indicate the marked changes for the amended specification and claims. Please provide all pending claims and amended specification with marked changes in response this Office Action.

In addition, on page 9 of the preliminary amendment, Applicants erroneously summarize that claims 1-42 are pending. Because claims 1-13 have been canceled by the preliminary amendment filed on 12/12/2003. the pending clams are 14-42. A appropriate correct of pending claims is required in response to this office action.

Election/Restrictions

1. Applicant's election without traverse of group IV, claims 22-39 in the reply filed on 08/12/2005 is acknowledged.

2. Claims 14-42 are pending. Claims 22-39 are considered. Claims 40-42 are withdrawn from the consideration.

Priority

3. It is noted that this application appears to claim subject matter disclosed in prior Application No. 10,066,130, filed January 31, 2002, now patent US No. 6,699,657B2. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or

119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

4. The information disclosure statements filed 11/18, 2004, 03/22/2004, and 04/20/2005 have been acknowledged, considered, and initialed. Applicants are welcome to provide the eligible copies of all non-patently literature (NPL) in the IDS submitted on 03/22/2004 since the application of 10, 066, 130 is not electronic filed. It is very inconvenient for reviewing all NPL in IDS contained in that application for the current application and in future child applications.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claim 25 is rejected because the claimed invention is directed to non-statutory subject matter of using a human as a screening tool of claimed invention. If it is an inadvertent

typographic error, an appropriate correct of claimed language is required in response to this Office action.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Moreover, claims 22-39 are rejected under 35 U.S.C. 112, first paragraph under scope of enablement, because the specification, while being enabling for a method to detect a RdRp virus replication by using a compatible eukaryotic cells that comprises a full length cDNA of RdRp virus or at least the cDNA comprising the gene encoding RdRp enzyme, does not reasonably provide enablement for a method to identify a compound or a condition by using any portion of the genomic sequence of a RdRp virus and by using claimed method without any comparative step for ruling out if the inhibition of the reporter gene is caused by a specific inhibitory effect against the RdRp viral enzymatic activity rather than a non-specific inhibition of reporter gene or host cellular metabolism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. The test of the enablement and scope of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following:

10. 1) & 2). Nature of the invention and level of skill in the art. The claimed invention is directed to an in vitro cellular assay model to identify a compound or condition that inhibits the

RdRp viral replication dependent on the RNA-dependent RNA polymerase mediated reporter gene assay. The method comprises to transfect a HCV infected cell line with a construct encoding an antisense reporter gene flanked with 3' and 5' RdRp viral UTRs in an antisense and reverse orientations. The reporter gene in the (-) strand is under control of the RdRp viral IRES.

11. 3). & 4). State of art and Unpredictability of the art. The state of art teaches that the positive single-stranded RNA virus comprises a nonstructural protein named RNA-dependent RNA polymerase (RDRP), which is required for the RdRp viral replicate in advance of the host cells. The Flaviviridae is one such type of virus. The Flaviviridae family comprises the flaviviruses, the animal pathogenic pestiviruses, the recently characterized GB viruses (GBV-A, GBV-B and GBV-C/hepatitis G), and the genus Hepacivirus or Hepatitis C virus (HCV). The RNA genome of these viruses typically includes a single long open reading frame encoding a polyprotein that is proteolyically cleaved into a set of distinct structural and nonstructural protein products. Translation of the open reading frame of the genome is directed via a 5' untranslated region (UTR), which functions as an internal ribosomal entry site (IRES). The 3' end of the genome in these viruses comprises a highly conserved UTR region of variable length, which is thought to be essential for replication. The most well-known member of the Flaviviridae family of viruses is the positive single-stranded Hepatitis C virus ("HCV"). The HCV polyprotein is a precursor to the individual HCV proteins necessary for replication, packaging and infectivity. The structural region of the polyprotein precursor (including the C, E1, E2 and p7 proteins) is processed by host cell signal peptidases. The nonstructural region of the precursor (including the NS2, NS3, NS4A, NS4B, NS5A and NS5B proteins) is processed between NS2 and NS3 by NS2-3 protease, while processing in the NS3-NS5B region of the polyprotein is accomplished by NS3 protease activity. HCV replication begins by viral penetration of the host cell and liberation of the viral genomic (+)single-stranded RNA from the virus particle into the cytoplasm of the cell. The viral RNA is translated by cellular enzymes, and the encoded viral polyprotein is processed into several distinct functional viral proteins including RNA-dependent RNA polymerase protein (RDRP). RDRP then proceeds to synthesize (-)stranded RNA intermediates (from template viral genomes) which in turn serve as templates for synthesis of new (+)stranded RNA molecules. These (+)stranded viral RNA molecules can then be used for further viral polyprotein expression, for synthesis of new (-)stranded RNA molecules, or for packaging into

progeny virions, which can then be released from the infected cell to spread the HCV infection. HCV NS5B is the RNA-dependent RNA polymerase essential for the HCV viral replication (See Cheney et al. Virol. 2002, Vol. 297, pp. 298-306). Therefore, an assay depended on the RdRp regulation requires the host cell comprising RdRp viral gene sequence. Moreover, the assay should also contain a step to rule out that the reduction of a reporter gene expression is caused by a specific inhibition of RdRp activity rather than a non-specific inhibitory effect(s) against reporter gene or other host cellular effect. Otherwise, it is unpredictable if a compound or condition, such as a compound or a temperature above 40 °C or below 17 °C may have a influence on a reporter expression or a host cell metabolism.

12. 5). The scope of the claims is directed to a method using any portion of the RdRp viral genome for running the assay and the assay as claimed without any steps to limit if the compound or condition influence the reporter gene or other cellular condition.

13. 6) & 7). Number of working examples and Amount of guidance presented in the specification. The specification only teaches that HCV infected cell line that is transfected with the a construct encoding a reporter gene in an antisense orientation flanked with the 3' and 5' UTRs of HCV respectively liked to the 5' and 3' of the sequence in an antisense orientations can be used for detecting HCV viral replication by measuring the reporter gene expression upon the viral RdRp gene expression. The specification also teach that three kinds of compounds categorized by inhibition of HCV protease, inhibition of RdRp enzyme and inhibition of reporter gene can all exhibit inhibitory effects against the reporter gene expression. However, the specification does not provide sufficient evidence to support that a viral compatible cell line transfected with any portion of a RdRp virus genome that is further transfected with a reporter gene can be used for detecting said RdRp virus replication and identifying compound or condition that inhibits said RdRp virus replication specifically. The specification is deficient for teaching whether the inhibition of the reporter gene expression by a testing compound is specific for the RdRp viral enzyme or other factors related to the reporter gene expression or even imagine, such as the compound D tested in example 3 of the specification or a temperature above or below the proper cell growth condition etc. There is not adequate guidance in the specification teaches which condition should be used for testing a specific influence against RdRp enzymatic activity that results in reduction of RdRp dependent viral replication.

14. Given the above analysis, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 22-24, 30, 31, 33 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Kovelman et al. (US patent No. 6,326,480B1).

17. Regarding to the antisense reporter gene construct, Kovelman et al. teach method for constructing a plasmid that comprises an antisense-reporter cDNA flanked at both its 5' and 3' ends with 3' and 5' UTR of said RdRp virus' gene also in an antisense orientations respectively.

18. Regarding to the method of identifying a compound using said plasmid to transfect a compatible cell line that is already infected or tranfected with said RdRp virus genome, Kovelman et al. teach a method comprises tansfection or transformation of suitable host cells with an antisense reporter gene plasmid as described above and co-culturing said host cells with the RdRp virus, preferably HCV virus isolated from a patient in the presence of a candidate compound and access the virus replication after compared with the predetermined level of the reporter gene expression in the absence of said compound. Kovelman et al. further discloses that within such method, after a suitable amount of time co-culturing the virus with said plasmid transfected host cells, the level of reporter gene expression can be evaluated in term of viral replication and evaluating the effectiveness of the tested therapeutic agent or candidate therapeutic agent (See entire document, especially, lines 3-48 on column 2, lines 44-67 on

column 3 and lines 1 –8 on column 4, lines 7-59 on column 5). While Kovelman et al. do not explicitly teach that the viral compatible eukaryotic cells are transfected cells with full length cDNA of said RdRp virus, the disclosure of culturing said plasmid transformed host cells at the present of said RdRpvirus, preferably HCV, indicates that the host cell inherently comprises said virus. Therefore, the claims are anticipated by the cited reference.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 22-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kovelman et al. (US Patent No. 6,326,480B1), Hagedorn et al. (US 5,981,247A) and Sherf et al. (US Patent. NO. 5,670,356A).

21. Claims invention is drawn to a method of identifying a compound or a condition that inhibits the genomic replication of a virus that depended on RdRp comprising culturing a virus compatible host cell line transfected with the cDNA of such virus and an antisense reporter gene construct comprising an antisense reporter gene sequence flanked at both 5' and 3' ends with 3' and 5' untranslated regions (UTR) of said RdRp virus reverse and antisense orientations respectively. The said construct further comprises a hepatitis δ virus ribozyme in the antisense orientation operably linked to the 5' UTR sequence, which functions to cleavage the unnecessary part for the activation of the RdRp initiated reporter gene activation. The reporter sequence is preferably selected from the group consisting of luciferase, beta-galctosidase, alkaline phosphatase etc.

22. Regarding to the antisense reporter gene construct, Kovelman et al. teach method for constructing a plasmid that comprises an antisense-reporter cDNA flanked at both its 5' and 3' ends with 3' and 5' UTR of said RdRp virus' gene also in an antisense orientations respectively.

23. Regarding to the method of identifying a compound using said plasmid to transfect a compatible cell line that is already infected or tranfected with said RdRp virus genome, Kovelman et al. teach a method comprises tansfection or transformation of suitable host cells with an antisense reporter gene plasmid as described above and co-culturing said host cells with the RdRp virus, preferably HCV virus isolated from a patient in the presence of a candidate compound and access the virus replication after compared with the predetermined level of the reporter gene expression in the absence of said compound. Kovelman et al. further discloses that within such method, after a suitable amount of time co-culturing the virus with said plasmid transfected host cells, the level of reporter gene expression can be evaluated in term of viral replication and evaluating the effectiveness of the tested therapeutic agent or candidate therapeutic agent (See entire document, especially, lines 3-48 on column 2, lines 44-67 on column 3 and lines 1 –8 on column 4, lines 7-59 on column 5). While Kovelman et al. do not explicitly teach that the viral compatible eukaryotic cells are transfected cells with full length cDNA of said RdRp virus, the disclosure of culturing said plasmid transformed host cells at the present of said RdRpvirus, preferably HCV, indicates that the host cell inherently comprises said virus. Kovelman et al. differ from the claimed invention in that they do not teach that the construct further comprises a cDNA of a Hepatitis δ virus ribozyme operably linked to the 5' UTR sequence in a sense orientation and the host cell comprises the SEQ ID NO: 18 of an reporter gene sequence.

24. Hagedorn et al. teach a method for screening a compound that inhibits replication of a HCV dependent on RdRp activity, wherein the method comprises constructing a polynucleotide construct comprising a delta ribozyme of hepatitis virus in addition of a reporter gene coding region in antisense (-) strand form, and an HCV IRES element, also in (-) strand form, wherein the delta ribozyme is configured to remove the 3' sequence unnecessary polyA tail of the antisense RdRp virus IRES incorporated reporter gene construct after transcription (Lines 7-48 on column 14). Hagedorn et al. also teach that such recombinant HCV-RdRp reporter gene expression construct canbe used for trasfecting a mammalian cell line that is used for assaying the effects of candidate anti-viral compound against RdRp activity (See lines 5-10 on column 3).

25. Regarding to the utilization of SEQ ID NO: 18, Sherf et al. disclose a reporter gene sequence that is 100 % homology to the reporter gene sequence of SEQ ID NO: 18 in the present

Application, the said reporter gene is modified to be more suitable and convenient for diverse applications (See lines 54-555 on col. 2 and Claim 4).

26. Because the notion of using an antisense-reporter gene construct for detecting a positive strain RNA virus replication that is dependent on RdRp activity is already taught by Kovelman et al. no matter which reporter gene is used as long as the reporter gene sequence is in the antisense orientation and flanked with both 5' and 3' ends of UTRs of said RdRp virus in an antisense orientation, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to combine the teaching disclosed by Kovelman et al. and Hagedorn et al. and adapt the luciferase reporter gene sequence disclosed by Sherf et al. to detect the replication of RdRp virus with or without a testing compound or condition absence of unexpected results. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BAOQUN LI
PATENT EXAMINER

Bao Qun Li Baoqun Li 10/12/2005